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Endocrine Effects of Combination Antioestrogen and LH-RH Agonist Therapy in Premenopausal Patients with Advanced Breast Cancer

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Abstract—*Thirty-eight premenopausal breast cancer patients were treated for periods up to 12 months with a sustained-release formulation of the luteinizing hormone-releasing hormone agonist goserelin [Zoladex, (D-Ser(Bu^t)^{6}Azgly^{10}-LH-RH); 3.6 mg depot every 4 weeks] either alone or in combination with the antioestrogen tamoxifen citrate (Nolvadex 40 mg/day). In both treatment groups serum gonadotrophin concentrations fell during the first month of therapy and were suppressed on continued treatment. In patients treated with the combination therapy FSH concentrations were significantly reduced in comparison with goserelin alone. Relatively normal ovarian activity was observed during the first few weeks of therapy. Thereafter, oestradiol and progesterone concentrations rapidly declined in both treatment groups. Slightly lower serum oestradiol concentrations were recorded in patients receiving combination therapy. No significant adverse side-effects were recorded in either group of patients.*

INTRODUCTION

THE non-steroidal antioestrogen tamoxifen citrate (Nolvadex) is well established as a first line therapy for the treatment of postmenopausal patients with advanced breast cancer. Response rates of approx. 30% in unselected patients rise to 50% in patients whose tumours are oestrogen receptor positive [1]. In randomized clinical trials in postmenopausal women, tamoxifen citrate was found to be as effective as high dose oestrogens [2–4], progestins [5–7], androgens [8, 9] and the aromatase inhibitor aminoglutethimide [10, 11] but to be without significant side-effects. Antioestrogens are also clinically effective in premenopausal women and bring about a similar objective remission rate to oophorectomy [12–15]. Tamoxifen citrate therapy, however, fails to suppress menstruation in the majority of patients [16] and has been reported to elevate circulating concentrations of oestradiol [13, 17, 18], which may contribute to disease relapse during antioestrogen therapy [18].

Recently, our group [19–25] and other laboratories [26–28] have reported on the clinical efficacy of another type of antihormonal agent in premenopausal breast cancer patients, agonist analogues of luteinizing hormone-releasing hormone (LH-RH). In contrast to the direct tissue actions of the antioestrogens [29, 30], LH-RH agonists are thought to act indirectly by suppressing gonadotrophin release from the pituitary gland and thus reducing the amount of oestrogen produced by the ovaries and ultimately available to the tumour [19–28]. The current paper examines the endocrinological effects of combining tamoxifen citrate and a slow-release formulation of goserelin in an attempt to reduce ovarian activity with the LH-RH agonist and counteract the residual actions of oestrogens with the antioestrogen. A preliminary study designed to investigate such combination therapy using the LH-RH agonist buserelin administered as a nasal spray failed to demonstrate continuous suppression of oestradiol and progesterone concentrations in premenopausal breast cancer patients. These observations, however, may be explained by an inability of the LH-RH agonist, when administered intranasally, to effect a successful medical castration [26].

PATIENTS AND METHODS

Patients selected for the study were premenopausal with histologically proven carcinoma of the breast who had either recurrent or locally advanced disease. No patient had received previous endocrine

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or cytotoxic therapy. Treatment was initiated at the breast clinic of R.W.B. Written and informed consent was obtained from all patients after full explanation of the protocol which had been approved by the appropriate hospital ethical committee. Tamoxifen citrate and goserelin were supplied by ICI Pharmaceuticals Division, Macclesfield, U.K. The sustained-release formulation of goserelin was a lactide–glycolide copolymer containing 3.6 mg of the LH-RH agonist in the form of a cylindrical rod 1.2 mm in diameter [31]. Two groups of patients were studied: Group 1 received goserelin alone (n = 24), while Group 2 received a combination of goserelin and tamoxifen citrate at a dose of 20 mg b.d. (n = 14). The studies ran sequentially with the same inclusion criteria applying to each group of patients.

Blood samples were withdrawn at regular intervals throughout therapy and assayed for luteinizing hormone, follicle stimulating hormone, oestradiol and progesterone using assay procedures previously described [23].

Statistical analysis

The data were analysed using the Mann–Whitney U test.

RESULTS

The data presented in Fig. 1 show that the continued exposure of premenopausal patients with breast cancer to the LH-RH agonist goserelin results in a decline in circulating concentrations of LH and FSH and a suppression of ovarian steroid hormone production. Thus, within 7–14 days of a subcutaneous injection of the sustained-release formulation of this drug a significant fall in the basal gonadotrophin values was recorded (Fig. 1a, b). Thereafter, the serum concentrations of LH and FSH remained low. On long-term therapy, serum FSH values showed a tendency to increase with time. Although serum concentrations of oestradiol and progesterone remained relatively normal throughout the first few days of therapy, they rapidly declined thereafter. In both treatment groups serum progesterone concentrations fell below the detection limit of the assay after 3–4 weeks of therapy (subsequent assay points not illustrated in Fig. 1c).

The combination of tamoxifen citrate with goserelin produced alterations in the circulating concentrations of the above hormones which were qualitatively similar to those observed with the LH-RH agonist alone. Serum concentrations of FSH, however, were significantly ($P \leq 0.05$) lower at all time points after 1 month in the combination group. Although this did not markedly influence ovarian function (Fig. 1c, d), pooling of the oestradiol data gathered beween 1 and 12 months, showed significantly ($P \leq 0.05$) lower serum oestradiol concentrations in the combination group. This effect was not observed following analysis of the oestradiol data during the first 28 days of therapy, nor was it observed for LH or progesterone. The side-effects of goserelin therapy alone included cessation of menstruation, hot flushes, vaginal dryness and occasional nausea. In patients treated with both goserelin and tamoxifen citrate similar side-effects were recorded.

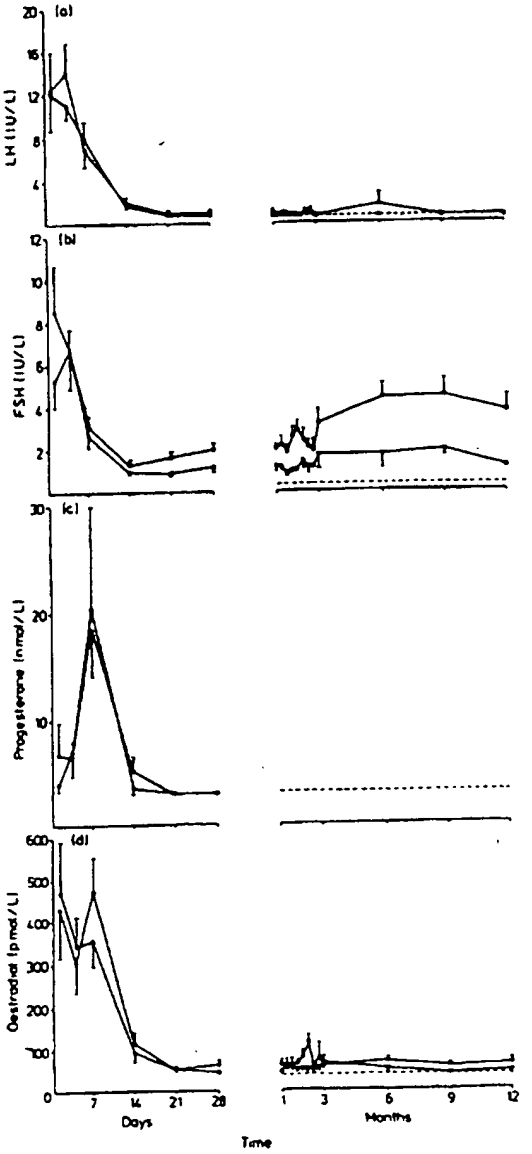

Fig. 1. Serum (a) LH (b) FSH (c) progesterone (d) oestradiol concentrations in premenopausal women with advanced breast cancer treated with a sustained-release formulation of goserelin (3.6 mg administered at 4 week intervals) either alone (○, n = 24) or in combination with 40 mg tamoxifen citrate/day (●, n = 14). The results are presented as the mean values ± S.D. Detection limit of the assay (---).

DISCUSSION

Previous reports from our laboratory have demonstrated that when the LH-RH agonist goserelin is administered to premenopausal patients with advanced breast cancer it rapidly results in pituitary gland desensitization to endogenous luteinizing hormone-releasing hormone, a fall in circulating concentrations of LH and FSH and a withdrawal of their support for ovarian steroidogenic processes [19–25]. This results in a rapid decline in the circulating concentrations of oestradiol and progesterone producing tumour remissions in approximately one third of unselected patients [21, 25]. The present study extends these observations to the combined effects of goserelin plus tamoxifen citrate and demonstrates that the antioestrogen has no adverse effects on the above events. Indeed, the combination therapy results in a more effective suppression of circulating concentrations of FSH and a further small, but significant, decline in serum oestradiol concentrations. These data, therefore, do not provide any evidence for a contrary interaction between LH-RH agonists and antioestrogens as had previously been reported by Klijn and De Jong [26] who failed to demonstrate continuous suppression of oestradiol and progesterone in patients treated with tamoxifen citrate and an intranasal formulation of buserelin. The failure of the above group to demonstrate a successful medical castration with buserelin, has recently been overcome by the use of twice-daily subcutaneous injections of the drug [32].

It is likely that the efficient suppressive action of the combination of goserelin and tamoxifen citrate on serum concentrations of FSH result, in part, from the partial oestrogen agonist properties of tamoxifen citrate [33] which has been shown to partially reduce gonadotrophin levels in postmenopausal women [17, 34, 35]. The greater reduction in oestradiol concentrations resulting from the combination therapy further supports the rationale of the study. Randomized clinical trials are currently in progress to assess the therapeutic efficacy of tamoxifen citrate and goserelin and goserelin alone in pre- and perimenopausal patients with advanced breast cancer. Although to date objective remissions have been recorded in both groups of patients it is too early to make rational comment on the relative clinical merits of these treatment modalities.

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